EXHIBIT 2

SpyGlass Group, Inc.

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Annandale, NJ 08801

EXPERT OPINION REPORT

QUALITY ASSURANCE & FDA COMPLIANCE

Actavis Inc.

Makers of Digitek

Summary of the Opinion

The SpyGlass Group, Inc. has determined that Actavis was not in complying with the FDA legal requirements for current Good Manufacturing Practice (cGMP or GMP) for at least the period of time, starting in XXX and ending with the Permanent Injunction of Nov. 14, 2008. During this period of time, the records demonstrate that …Because of gross violations of Good Manufacturing, for this period of time, the production, control and quality processes for Digitek was not able to consistently and reliably manufacture products that meet legal requirements and suitable for commercial distribution.

As a result of multiple FDA site inspections, Actavis was issued a Form 483 (notice that identifies significant deficiencies in their Quality System). As a result of not taking swift and effective corrective action, the FDA escalated their public concern by issuing multiple FDA Warning Letters. Actavis did not effectively correct the deficiencies identified in any of the FDA mandates. After being given every opportunity to correct their deficiencies, the FDA permanently closed their doors to any further manufacturing. This type of severe legal action on a United States drug company is exceedingly rare.

Actavis was repeatedly warned by the FDA representatives and patient complaints, but failed to take adequate action ultimately resulting in the permanent closure of their plant. The FDA has stated…substandard product…. Our review of the evidence confirms the FDA's conclusion.

Based upon Actavis' actions indicated in the records, product-out was a first priority, meeting legal and patient obligations was secondary.

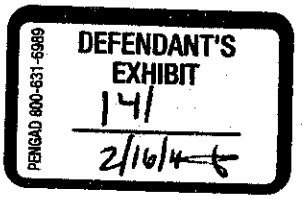
Based upon working with hundreds of diverse medical products companies we can state that no company (within these hundreds) has so blatantly and consistently disregarded their legal and patient obligations.

by

Mark G. Kenny

Salvatore J. Romano PhD

1 – January – 2010



Introduction

The SpyGlass Group, Inc.[1] was contacted by the law firm Motley-Rice, seeking an expert in Quality Assurance and current Good Manufacturing Practice (cGMP)[2] to provide expert opinion in regard to a legal action against Actavis Inc. (formerly known as Amide), a manufacturer of drug products.

Mark G. Kenny & Salvatore J. Romano PhD have been engaged by Motley-Rice to prepare an expert report, participate in a legal deposition and testify as an expert witness in a trial. Our expert opinion is based upon on over 75 years experience in:

- Running the Quality Assurance and Compliance Programs for multiple medical product manufacturing companies (from small start-up companies to large, multinational companies)
- Objectively and fairly auditing hundreds of domestic and international medical products companies engaged in the development , manufacture and distribution of products regulated by the FDA
- Determining the potential adverse effects that noncompliance has on the product quality and the customer's trust in the product
- Reporting to senior management, risks associated with faulty control systems
- Understanding industry standards commonly used to comply to cGMP
- Reviewing quality records for the purpose of identifying potential violations to cGMP
- Investigating root cause of noncompliance and recommending reliable fix
- Creating effective corrective action programs for many companies in serious violation of cGMP, subsequently eliminating public health risks

This expert report is being co-developed by Salvatore J. Romano PhD and Mark G. Kenny. It is our belief that a more objective and experienced-based report will result from this collaboration.

[1] See Appendix X
[2] See Appendix Y

1. WORK PLAN

Approach

- Review documented evidence applicable to the scope of the assignment
- Prepare an expert witness report that documents our findings
- Participate in future legal proceedings which may include deposition(s) and a trial process
- Information Utilized

Quality and Control Systems

- To determine whether or not that products made at their facilities meet cGMP.
- To determine (through examination of the documents available and a plant visit) whether or not Actavis complied with cGMP and meet the requirements for identity , strength, quality and purity that they purport to have and are fit to be released
- To prove by examination of the documents available and a plant visit that all the products made at their facilities do not meet cGMP. To show that Digitek was released with an oversized tablet problem that Actavis/Amid never understood over this period and this caused serious adverse drug reactions in patients taking this drug.
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Product Quality

- To determine whether or not Digitek was released with an oversized tablet problem that resulted from gross deficiencies in their Quality Systems.
- To determine whether or not Digitek (digoxin) tablets made over the period of Nov. 6, 2003 to Nov. 14 2008 meet the requirements for identity, strength, quality that they purport to have and were fit to be released for sale to the marketplace.
- To determine if Actavis/Amid understood over this period and this caused serious adverse drug reactions in patients taking this drug. Evaluate various FDA Inspection Results and internal documents associated with the manufacture, test and release of drug products to determine whether Actavis, Inc. was or was not in compliance to applicable FDA Regulations (cGMP), FDA guidance documents and industry standards
- Determine the effect of Activis' compliance performance has on the quality of drug products distributed to the public
- Determine the likelihood that Actavis has or has not released product that violates FDA Regulations

2. INFORMATION UTILIZED

- Documents gathered by Plaintiffs in the form of FDA reports, 483's, EIR's, Warning Letters, Consent Decrees, and a Permanent Injunction
- Internal Actavis documents such as batch records, investigation reports, memos, & E-mails.
- Depositions of individuals working for Actavis and Mylan
- Plant visit –??????????????????????

3. Summary of Opinion

MGK Organize this by subjects.....Needs work in general

QUALITY AND CONTROL SYSTEMS

A detailed analysis of the cGMP Compliance history of Actavis was performed by the Spyglass Group for the period of 2/8/06 to 5/20/08. FDA observations were classified into five systemic areas of concern: Quality System, Facilities & Equipment Systems, Production System, Laboratory & Control System, and Regulatory Requirements. Numerous areas of repeat observations by FDA over several years indicated that Actavis was grossly noncompliant with cGMP. Although FDA gave Actavis every opportunity to correct deficiencies and resume normal operations, they never "got it". Therefore critical systems that control the Quality of the product, were substantially and constantly out of compliance and operating in a high risk environment. There was no apparent attempt to mitigate the product quality risks through extra testing, inspection, etc. In our opinion (backed by FDA action) Actavis should not have been releasing product in their New Jersey manufacturing plants. This came about by the Federal Government in the form of a Permanent Injunction on 11/14/08 (?date?) that shut down all operations.

FDA COMPLIANCE TO GMP

PRODUCT QUALITY

For Digitek digoxin tablets made by Amide and then Actavis Pharma, there was a known problem with thicker than normal tablets on 7/7/04 when a customer complaint was received with a double thickness tablet. The root cause of the double thickness problem was never identified. The defective double thick product resurfaced again in 3/18/08 when an FDA inspection identified a batch with a known double thickness problem that was released for sale under a deviation. Again, Actavis failed to find the root cause of the double thick defective product. In our experience it is common practice in the pharmaceutical industry to reject such a batch immediately without the possibility of reworking it. In our opinion the Digitek production process was unreliable and not properly validated to produce product fit to be released for sale into the market place that met requirements for identity, strength, quality and purity as specified by cGMP.

4. A Primer on current Good Manufacturing Practice FDA Regulations & Quality Controls

What is GMP?

Good Manufacturing Practices (GMP or cGMP) is an expertly crafted law that is established in the Code of Federal Regulation. It represents the minimum requirements in the Drug Industry for producing a product that meets all… The law was originally drafted for comment by the FDA using industry acknowledged experts. Industry experts then commented on the content of the draft proposed regulation and in an iterative process, a law was established that outlines the requirements for every drug manufacturer to follow. It has been continually improved (via the same methodology, i.e. industry participation) since its' approval in 1973? My opinion (which is shared by most industry Quality & Compliance leaders) is that it is well designed document and of great help in ensuring that patients and customers receive 100% safe and effective drug products. In fact, most Quality & Compliance leaders, to continue to place GMP in business terms, frequently refer to GMP as "good business practices." Likewise, it is my experience that the FDA understands our business and fairly and impartially uses a heavy-hand only when they fear public safety. In these high-risk situations, they continually escalate their concerns until all public risks are resolved.

Why is GMP Important?

It is important to understand that the term "Good" is somewhat misleading, GMP is the legal minimum and it is not optional. My opinion (which is shared by most industry Quality & Compliance leaders) is that significant breakdowns of the Quality and Control Systems (established in this regulation) will inevitably result in serious product quality risks; more specifically, "bad product" being released to the American public.

Why is the FDA Requirement of Investigating and Corrective Action So Important?

All of the controls established in the GMP Regulation are important; however, some are more important than others. The concept of Corrective Action and Preventive Action (CAPA) is critical.

CAPA is a procedure is a disciplined and comprehensive approach to resolving problems permanently. When errors (referred to as nonconformances) are discovered in any of the Product Quality and/or Control Systems, industry, by law must investigate. This is common sense to most people, i.e. when you find a problem you need to understand the seriousness of the problem and resolve the situation accordingly. Some nonconformances are important but not urgent. Other nonconformances require immediate investigation, including notifying top management. This practice is somewhat similar to the triage procedure used in a hospital emergency room. For example, if manufacturing equipment were to produce products that had cosmetic issues (e.g. slight crooked printing) of the carton lot number, this is important but not necessarily high risk. The operator has the authority to make an immediate adjustment on the equipment and (with Quality Assurance oversight) inspect the product made, determining when the problem occurred and potentially culling out the defective cases for immediate rework. This type of occurrence would generally not require the immediate notification to top management. On the other hand, if defective tablets (for example double thick) were being discovered at any point in the manufacturing process, immediate actions would result. This is a highly disciplined procedure. It is likely that many of the following actions would be performed;

A. The production line would be stopped and not restarted until a complete investigation were performed (in accordance to an detailed control procedure).
B. This category of defect, i.e. oversized or potentially mixed tablets, creates the highest order of concern for the company. Any suspected suboptimal control system that could result in this type of defect is what keeps Quality Assurance Directors up all night.
C. The Manager of Quality Assurance and Manufacturing would be notified immediately

D. A formal and documented investigation would begin (in accordance to another detailed control procedure)
E. Based upon the preliminary investigation, that lot number would be placed on hold and segregated, identifying the product as potentially defective. Additionally, the batch would be identified in the computer inventory control system as on Hold or Quarantined, thus eliminating any chance for the premature release of the potentially defective product. Classifying the the product lot as "On Hold" and later reclassifying a product lot as "Accepted" is a key control step. Quality Assurance is the only one that has the electronic "key" to change these product lot classifications. Unless a worker purposely mishandles defective product, it is almost impossible , in current computer inventory control systems, to generate the necessary paperwork to release a batch for sale.
F. A full-scaled documented investigation would follow, ascertaining the specific (root) cause of the nonconformance. The investigation would extend into many of the control systems within the company, far beyond some of the obvious potential causes. As part of the investigation, a determination would be made as to the acceptability of the batch.
G. After the documented investigation has determined the root cause, a specific documented corrective action program would be designed and deployed.
H. All of this would be in strict compliance with GMP and other FDA Guidance Documents

During an FDA Inspection, the CAPA system and records are generally reviewed to ensure that the company's practices and procedure comply with GMP. The FDA has determined that this is a focus area during their audits. In a similar fashion, product complaints are handled with the same level of attention, documentation and follow many of the principles associated with CAPA.

What are the Results of Not Following GMP

Generally there are several potential outcomes:

A. FDA Issues - FDA inspections discover the lack of GMP Compliance and determine the seriousness of the complying practices. They then determine to report their findings with no further inspection, or continue to inspect until they are satisfied that they understand the relative company risks. Should the situation warrant it, the FDA will continue to escalate their actions to FDA Form 483, Warning Letter(s), Product Recalls, or worse, including the permanent shutdown of manufacturing (Permanent Injunction). Permanent Injunction is highly rare and represents the FDA's highest order of concern. They are exceedingly rare.
B. Manufacturing Problems – GMP describes fundamental controls that are necessary to be in business. Most of the top companies in the world (regardless of product category) practice these abide by these principles and deploy them exceedingly well. Those companies that do not or have significant lapses in sustaining these procedures are doomed to have product recalls, e.g. Toyota. Companies that experience GMP problems are continually "fighting fires", constantly being faced with nonconforming product and nonconforming practices. Most Quality Assurance professionals will agree with this statement.
C. Product Quality – Product quality will always suffer when GMP is not established. The worse the systems, the worse the problems. Each product defect (originating with complaints, production line, packaging line, etc.) needs to be formally investigated. When a company is constantly fighting these type of fires, there are never enough people to manage the fires. The result is that the problems are ignored or the investigations are superficial, having little chance to determine the root cause and less chance to implement an effective and sustainable corrective action. The lack of effective control systems is the common root cause of almost all product defects. The lack of effective control systems will result in the release of product that does not meet… and is unfit for human use. When this type of product is discovered or the quality is suspect, a responsible company will Recall the product. .

What are Some of the Critical Systems & Controls in Drug Manufacturing?

Batch Record: This is a compilation of all of the vital records and results that provide evidence that the production lot/batch was manufactured and tested in accordance to approved procedures, test methods and specifications. It is also evidence that a batch complies with any FDA submissions. It is a stand-alone document, which means that it should be understood by any experienced reviewer without any significant explanations. It must be complete. The document must include the records previously mentioned plus any exceptions. Exceptions would include issues that were encountered during the manufacturing or testing of a batch. For example the following documentation is required to be in the batch records: out of specification reports, CAPA reports, rework or salvage records, etc. The final control step, before the product is released to market, is the independent Quality Assurance review. This person's responsibility to certify in writing that the product was manufactured and tested in accordance to the approved procedures and the test results meet all specifications. The final record is then properly stored.

Out of Specification Test Result (OOS): If a lab analyst performs a test and discovers out of specification results, then the analyst must follow a strict procedure which involves a formal and documented investigation. The initial first results cannot be automatically disregarded. The strict procedure has built in controls to ensure that the final test results are correct. An OOS is a significant occurrence that requires critical thinking and investigation to properly resolve. The documentation associated with the event must be carefully documented in accordance to the procedures. Failure to follow the OOS procedure will yield results that may be incorrect, ultimately allowing unacceptable product to be released to the market.

Nonconformances: When a manufacturing or Quality assurance action does not meet the approved procedure then a nonconformance occurs. When a test is performed and the results do not meet the specifications and/or the documented requirements, then a nonconformance occurs. Nonconformances are required by law to be investigated and handled in accordance to approved procedures.

Good Documentation Practice: This is an informal term for a highly formalized controls. All recorded information must be clear, legible and understandable. When an error is made by an associate, the error must be handled in accordance to procedure. There will be signed and approved signatures next to every change is results. There is legal code of ethics that all information including dated signatures must be honest. All documents requiring approval, e.g. CAPA, must be signed by all of the technical and management associates as required by the procedure. There is no exception to this rule. Any records that are not honest are falsified records. Any unapproved/unsigned and undated documents are not acceptable records and almost unusable (without a written investigation that states the reason they are unsigned and then resigned by all of the required approvers). The final Quality Assurance review is intended to discover Good Documentation Practice nonconformance and hold the batch until a documented investigation is conducted, again in accordance to approved procedures. This is not a nice to do, it is the law.

Corrective Action and Preventive Action (CAPA): CAPA is a highly disciplined procedure that is initiated after a preliminary investigation is conducted. The CAPA is intended to understand the seriousness of the problem (nonconformance) and handle the situation in a responsible and ethical manner. As with all of these type of occurrences, documentation is required from the beginning of discovery through the end of the CAPA process. A CAPA is initiated when a nonconformance occurs; for example, when a double thick tablet is discovered mixed in acceptable tablets. Using this as an example, the manufacturing would normally be stopped completely. All product manufactured up to that date will be quarantined/held in accordance to approved procedures. Managmenet would be notifed and an investigation leading to a CAPA would be initiated. This type of occurrence (e.g. mixed product, oversized tablet) etc. is among the most serious issues and requires impeccable investigation and documentation. All potential factors must be investigated, not just the obvious. For example, when someone is inspecting for the correct printing of a label on a moving production line and it is discovered that the operator missed an unprinted label. The immediate implication is that the person is not performing their job. When in fact, an investigation might have determined that it is physically impossible to adequately perform that investigation due to human limits. A further investagition may uncover that the pinting equipment is not capable and reliable and must be redisgned to produce an acceptable label. A short-term corrective action (since the root cause is the printing equipment) would be the addition of a failsafe computer vision device to inspect each and every label, mechanically removing any label that fails the inspection. It is important to understand that for critical defect nonconformances (such as double thick or mixed tablets) the corrective action phase must be fool-proof. This is not a nice to do, it is the law.

Complaint Handling: Each complaint must be investigated (unless there was a prior adequate investigation performed on this complaint issue). There is a disciplined procedure that requires a series of events to take place. These events associated with an investigation may include (but is not limited to):

- Examination and chemical testing of the complaint sample
- Examination and testing of product retain sample(s) (retained product samples are required to be selected from every batch and stored in a controlled manner, intended to help investigations into future problems)
- Review of prior complaints with the specific batch
- Review of prior complaints with this specific product and similar products (If there is an issue, it must not be automatically be assumed that the problem is only affecting the complaint batch)
- Trend analysis
- Inspection of the Batch Record and other records
- Interviews with manufacturing and Quality Assurance
- Review of studies performed, for example equipment qualification studies, process validation studies
- Review of the adequacy of the current procedures and specifications
- Review of the stability testing results
- Etc.

If the investigation determines that there might be unsafe product in the marketplace, then the investigation must be escalated to top management and a recall decision must be made. This must be conducted in accordance to procedures and FDA Regulations. Some of the activities and documentation may have to be submitted to the FDA for their review.

5. Expert Opinion

5.1. Actavis Corporate Culture

- The Corporate culture was production at any cost and ignore the Quality Systems. The CEO said in regard to process validation: " We don't need to practice making tablets"....(get exact name & quote, & ref.). There seemed to be an attitude of using Quality Systems and QA as window dressing for the FDA and not taking GMP seriously.

Conclusion:

5.2. Actavis Management

- Corporate and QA management were weak and not knowledgeable of the cGMP
- Many drug products were made and sold without approved NDA's /ANDA's showing arrogance or a complete lack of knowledge of Regulatory Requirements.

Conclusion:

5.3. Mylan Obligations

Mylan Obligastions

- Internal & Mylan GMP audits were apparently not done and, in Mylan's case, only one was done and a poor one at that. (Mylan audit ref.) Mylan was negligent in controlling its contractor Actavis. Lack of visits, audits and followup.

Conclusion:

5.4. Product Quality

Product Quality

This section of the Report will show that a double thickness problem in Digitek existed from at least 7/04 until 12/ 2008, maybe later. It will question the wisdom in the decision to release Digitek, digoxin 0.125 mg , Batch # 70924 for sale and show why it should have been rejected and destroyed. It will show why the investigations conducted are inadequate and a root cause determination was never made. It will show that adequate corrective action was not taken, since the root cause of the problem was never determined. You can't fix when you don't know what's wrong with something.

This section reviews the following incidences:

1. Discovery of a double thick 0.25 mg Digoxiin tablet

2004 Report of Double Thickness Tablets

[redacted]

Discussion:

Investigation Report 04-003 summarizes the results from a customer complaint received by Amide Pharma on 7/7/04. A pharmacist returned a 0.25 mg Digoxin tablet from Batch # 3611A which was approximately twice normal thickness and weighed twice as much. The investigation of the process records showed no out of specification results. Two Stokes compression machines were used on Batch # 3611A. Under normal operation these machines cannot make double thickness tablets. Upon machine set up however, double thickness tablets can be made, are observed by the set up operator who adjusts the machine and clears the area of any double thickness tablets prior to actual production startup. A single batch of digoxin tablets can take several days to compress. Investigation 04-003 concluded the most probable cause of double thick tablets was that they were made during the initial setup , the single tablet returned became stuck in the deduster and was not removed or detected prior to starting the production run. As a normal production process for digoxin, tablet compression is stopped and restarted for breaks, shift changes and overnight. Line clearance and QA inspections do not occur for restarts.

Investigation of Investigation Report 04-003

- Critical Document is Unapproved and Undated - The Investigation Final Report is not signed and dated. This is a gross violation of cGMP. (do we have the "official" doc ?)
- Approval by Top Management: The Investigation Final Report was never approved by Senior Management as required by the SOP. Management includes:
  - Quality Assurance Director
  - Vice President Scientific Affairs
  - Manufacturing Operations Director
- Corrective Action Dates – There are no dates associated with the corrective action
- Analysis of the Complaint Sample: No analytical testing of the complaint sample
- Critical Corrective Action - Verification of corrective action is documented; however, records of the Production and QA Departmental Operating Procedures indicate that not all of the corrective action was implemented as stated. One of the few stated corrective actions required that the manufacturing operators will clear the dedusters by operating the deduster vibrators at the maximum vibration setting. The SOP's were never updated to reflect this requirement. (can we prove this?)
- Document Revision History – All of the referenced SOP's had the past revision records, making traceability of requirements almost impossible
- Undisciplined & Inadequate Investigation – The root investigation do not follow any generally accepted problem solving method. The root cause was never identified, yet the investigation only focused on cleaning the deduster and chutes at start-up. There are many more potential root causes that were not considered.
- Inadequate Corrective Action – The corrective action was not effective as was evidence by a repeat double thick tablet incident (Lot 709241A1/A2)

During the investigation, it was not reported whether or not detailed laboratory analysis of the returned tablet was done, only thickness and weight measurements were made. It is not reported whether or not attempts were made to duplicate conditions on the compressions machine that would make double thickness tablets to better understand how to prevent it in the future. There may be many ways for one or more double thickness tablets to be made, be found in the finished bulk tablet buckets and contaminate the entire final packaged batch.

Apparently no retained samples of this or other lots were inspected to see if they contained double thickness tablets. The double thickness tablet complaint was classified as an isolated incident and the investigation was closed.

A prudent company would have reevaluated and revalidated the process using pharmaceutical development people . Process simulations should have been attempted to reproduce the defect to better understand and prevent the defect from happening in the future.

Conclusion:
XXXXXXXXXXXXXXXX

2007- 2nd Report of Double Thickness Tablets

[redacted]

DISCUSSION

Continuing on with the history of double thick tablets, Amide Pharma and then Actavis Pharma experienced many FDA GMP Compliance issues resulting in FDA 483 citations and Warning Letters for the period of 2004 to 2008. Some of these citations were caused by compression problems.

The double thickness Digitek problem surfaced again in 11/12/07 with Batch # 70924A1 of 0.125 mg digoxin tablets when during packaging, 5 tablets of approximately double thickness tablets were found by packaging operators. The details of this batch are found in the Batch Record (P #???) and in Investigation Report # 07-093. This batch was put on hold and subsequently 100% inspected visually. (See 07-093 Attn. # 6) A total of 20 double thickness tablets were found in the batch. The locations of all the double thick tablets in the batch was not identified, but the distribution appears to be random. (find the bucket #'s !! in docs). A tightened AQL inspection of the batch followed. No new double thickness tablets were found. The batch was released under deviation for packaging /sale.

FDA issued a 483 on an inspection of 993 Riverview Dr. from an audit from 3/18/08 to 5/20/08 with 11 major observations. Observation 2 states that " Drugs products fail to meet established specifications and quality control criteria are not rejected". Specifically it states in 2 a. " During packaging of Digoxin Tablets 0.125 mg, lot #70924A1 , five double thick tablets were observed. Quality Assurance approved a 100% visual inspection of the 4.8 million tablet lot which resulted in an additional 15 double thick tablets. Although Quality Assurance was aware of the "double thick' tablet findings, the batch was then released based on AQL sampling which included visual inspection of 1330 tablets. No root cause was determined for the defect; however the lot was released to the market by the Quality Unit on 1/28/08 following the visual inspection. There was no documented evaluation of the approximately 89 lots remaining on the market at the time of inspection". Here the FDA is stating that Batch # 70924 should have been rejected and all remaining 89 lots in the field be recalled.

Initial Events

NEED TO FILL IN

Unexplained Decisions

- When the defective tablets were later discovered in packaging, the packaging operation was allowed to continue. Shouldn't the batch have been halted and all materials placed on hold for a comprehensive investigations?
- On 12/4/2007 finished uninspected finished product lot containing defects was released for sale by Quality Assurance. A day later (12/05/2007), QA reversed their decision and decided that the batch was not acceptable and should not be distributed. The distribution of the lot was halted and the product lot was placed back on hold without any documented reason for this action. The batch was subsequently salvaged by breaking down the package, saving the tablets, visually inspecting the lot to eliminate defects, repackaging and then re-releasing the salvaged batch. The justification for these actions was not documented.

Inadequate Quality Problem Investigation

- Root cause of the problem was never confirmed but "appeared" to be caused at compression machine startup.
- Tablet compression was on 2 Stokes Presses over a 3 day period. The presses were stopped a total of 18 times for breaks, lunch, and overnight with no QA checks on restart. Stoppages ranged from 20 min. to 17 hr.
- A total of 20 double thick tablets were found in the batch, apparently randomly disbursed in the batch.

Five were found in Packaging—buckets #15 &#16 (2), #17(1), #34(2) and in 100% inspection another 15 with no locations noted. How could these all be the result of startup?

- Investigation is incomplete and never included other potential root causes to the production of double thick tablets, including:
  - There is no documented investigation into complaint history for similarly manufactured tablets
  - Double thick tablets were never chemically tested. The dose of the double tablets is not known.
  - No review of records to determine if the equipment is qualified and the process validated
  - No review of the training records of the associates
  - No consideration of design changes to the equipment to eliminate future defects
  - No review of the proper use of defect buckets and labeling practices
  - No discussion of the history of this type of nonconformance ??? confirm
  - No clear conclusions resulting from the investigation
  - No subsequent increase in QC checks at startup or processing, despite the fact that they do not know the clear root cause
  - No investigation into the history of change of the equipment
  - No review of the preventive maintenance of the tableting equipment
  - No review of the other 167 (#???) lots of Digoxin tablets on the market within expiry

<u>Ineffective and Unreliable Methods to Salvage a Known Defective Tablet Batch</u>

- Production and Quality Assurance used a method to salvage a defective batch (containing double thick tablets) that is generally not accepted in the drug industry as being effective, i.e. their method for culling out 100% of the defects within a 4,800,000 tablet batch through human inspection. This method of visually inspecting out defects is known throughout the medical products industry to be unreliable. It is frequently quoted within industry that 100% inspection is no better than 85% effective (80 %!!!). 100% Inspection is not 100% effective. It is certain that further defective tablets remained in the batch. (Ref. Juran and Craig QP 2004 July) In fact experts in the QC field state that " the human inspector finds about 80% of the defects present and misses the remaining 20%." Therefore if 20 were found, 5 still remained in the batch which would cause a problem for the patient that takes the double strength tablet. (check this math!!!)

- After 100% inspection, the batch was subjected to another QA inspection using a tightened AQL where each of the 34 individual buckets from the batch were randomly sampled with 40 tablets each.
  The sample and test plan was as follows: AQL level = 0.065, Sample Plan= single, tightened level 1, Sample Size Code = Q, Bulk Size ~ 4.8 million, Inspect 1250 tablets minimum from 34 drums. 40 from each of 33 drums, 10 from 34th drum. Tablets taken at random, Accept on 1/reject on 2 of total batch.
  After visual inspection, a Quality Control sample inspection was designed to allow less than 100% effectiveness. The batch could be released even if a defect was found in the final QA samples (i.e. the lot would pass if one (1) defective tablet was found in the samples, only rejecting if two (2) or more defective tablets were found.) The "tightened " AQL testing plan would have released the batch even if one defective tablet were found.

  - There is no documented procedure that describes the equipment, techniques and methods used in the inspection
  - There was no Quality Assurance monitoring of the visual inspection.
  - There is no documentation that the inspectors were trained on the inspection method
  - The salvage method was not properly approved. There was no approved Deviation Record to authorize the procedure of tearing down finished product and 100% inspecting.
  - There is no record that the visual inspection procedure is effective. The procedure was never qualified.
  - The acceptance criteria for 100% inspection were not established.
  - After salvage of the batch, the quantity of bottles increased by 2 bottles. The quantity would have been expected to decrease because of the double thickness tablets that were removed. There was no record of this deviation in the batch records for the increased size of the batch. An <u>undated and uncontrolled</u> memo from Dave Ashesh to Scott Talbot (date field left blank) provides potential reasons for a discrepancy. This memo is not included in the original Batch Records.

<u>Inadequate Batch Record Detail of the Lot Salvaged Through 100% Inspection</u>

- There is no documented evidence that the defective lot was properly salvaged. For example, the following required information was not included in the batch record:
  - Inspection Start and End Date/Time

- Name and document number of the 100% inspection procedure/method
- Startup inspection
- Clean up inspection
- In-process Quality inspection monitoring
- Inspector names
- Inspector training records
- Deviation authorization number

- The inspection protocol did not include the required information, for example:
  - Inspection Procedure
  - Acceptance Criteria and Specifications
  - QC Sampling Plan
  - Responsibilities
- Batch # 70924 Should have been rejected because there is no confidence that the process was capable of producing defect free tables and the QA inspection process could not remove all defective tables produced.

SPYGLASS GROUP CONCLUSION

- The methods and procedures in place during the production of Lot 709241A were not in compliance to FDA GMP Regulations.
- Significant violations of GMP contributed to the production of a lot containing critical defects, i.e. "double thick tablets".
- After the discovery of tablet defects, the lot was not destroyed. It was further processed using ineffective and unvalidated methods that would not have provided a high level of assurance that the lot was defect-free.
- The later problem investigation never conclusively determined the root cause of the problem.
- The investigation was not thorough and comprehensive or in accordance to the regulatory requirements.
- Because the investigation was inadequate, the corrective action may not be effective in preventing recurrence of the double thick tablets.
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5.5. Actavis GMP History with FDA

Actavis cGMP Compliance History with FDA

5.6. Quality Systems

Quality Systems

- Deviations and investigations were not closed out in a timely manner. (p 216) So many deviations/investigations.
- FDA said that from a Quality Systems standpoint, there was "Total Failure" (p 106)
- Corrective action team did not show up for team meetings. No sense of urgency. (p 95)
- Corporate greed. " worst case-cash flow" (p 197)
- Wanda Eng's comments on GMP/QA (p 146) (need some comments on her E-mail)

This lack of GMP knowledge is "all rather sad" (p 147)

Conclusion

5.7. PLACE KEEPER

5.8. PLACE KEEPER

5.9. PLACE KEEPER

Overall Observations of the Quality System at Actavis

Finally in the Digitek matter, the Federal Government cited Actavis Pharma for serious GMP violations in 5 FDA inspections over a period of 2006 to 2007 issuing a "Complaint of Permanent Injunction" on 11/12/08. This Injunction shut down all production and sales of products from all of their NJ locations. In paragraph 21 of the Injunction, the FDA inspection of 3/18/08 to 5/20/08 was noted. Item 21.2 states that Actavis failed to reject drug products (including Digitek Batch # 70924) failing to meet established standards or specifications and any other relevant quality control criteria, 21 CFR, 211.165(f). It is clear that Actavis was not capable of making drugs , including Digitek dioxin tablets , that comply with cGMP from 11/12/08 at the time of the Injunction going back to at least 2003.

6. Appendicies

- **References & List of Documents Utilized**
- (this needs to be organized better….need to number them and them list them in the text with the appropriate #)
- Digitek Digoxin Tablet – Documents to support opinion
- 7/9/04 Pltfs Exhb # 128, Amid Pharma Investigation Report # 04-003. Complaint of double thick 0.25 mg tablet.

- 1/10/06 Pltfs Exhb #79, FDA 483, observation # 8 on compression problems.
- 8/15/06 Pltfs Exhb# 35, FDA Warning Letter, ADE's and no ANDA's
- 2/1/07 Pltfs Exhb# 25, FDA Warning Letter, revision of # 35
- 4/07 ???? Pltfs Exhb# ???, APR 2007 for 0.125 mg Digoxin including Batch # 70924 as being released
- 11/12/07 ?? Pltfs Exhb# ??? Batch Record # 70924
- 12/5/07 Pltfs Exhb# 16, Investigation Report #07-093, Batch # 70924, double thickness
- 3/18/08 Pltfs Exhb# 26, FDA 483 , Batch # 70924 etc.
- 3/18/08 Pltfs Exhb# 91, FDA EIR, inspection of 8/18 to 5/20/08.
- ??? 2008 Pltfs Exhb# 144, APR 2008 0.125 Digoxin.
- 11/14/08 Pltfs Exhb# 82, Complaint of Permanent Injunction.
- Quality Control Handbook, J.M.Juran, 3rd Ed. , 1951, McGraw-Hill, pp. 12-61 to 12-63. On 100% Inspection Accuracy.
- Quality Progress, D.J.Craig, July 2004. On 100 % Inspection Accuracy.

Overall Observations of the Quality System at Actavis

(Mark… We need to write a dialogue followed by bullet points on the following;)

- The Corporate culture was production at any cost and ignore the Quality Systems. The CEO said in regard to process validation: " We don't need to practice making tablets"….(get exact name & quote, & ref.). There seemed to be an attitude of using Quality Systems and QA as window dressing for the FDA and not taking GMP seriously.

- Corporate and QA management were weak and not knowledgeable of the cGMP

- Many drug products were made and sold without approved NDA's /ANDA's showing arrogance or a complete lack of knowledge of Regulatory Requirements.

- Internal & Mylan GMP audits were apparently not done and, in Mylan's case, only one was done and a poor one at that. (Mylan audit ref.)

- Mylan was negligent in controlling its contractor Actavis. Lack of visits, audits and followup.

- Deviations and investigations were not closed out in a timely manner. (p 216) So many deviations/investigations.

- FDA said that from a Quality Systems standpoint, there was "Total Failure" (p 106)
- Corrective action team did not show up for team meetings. No sense of urgency. (p 95)
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Review of Actavis GMP Compliance History—All Products

(Mark….I have added your stuff on GMP please add some dialogue……I did not do a good fit of all of your tables into this doc ! Maybe the table detail should be as an attachment ? I think the following section on Digitek is good….can you get this section in the same bullet format?)

SPYGLASS GROUP CONCLUSION RESULT OF FDA DOCUMENTATION

- cGMP Systems – The FDA identified every significant cGMP System Category in the cGMP regulation as grossly noncompliant
- Systematic Approach - After being notified of serious violations – there was no systematic corrective action
- Management's Lack of Action - Repeated violations indicate that Management either ignored or were ignorant of the legal requirements of the cGMP regulations
- Qualified Quality Management - Not aware of any Quality Professional that would have allowed their organization to repeatedly ignore the FDA's strong messages
- FDA Impartial Approach – FDA appeared to have given Actavis every opportunity to resume business as normal, provided that a company-wide cGMP improvement program was implemented. Actavis never got it!

7. Findings

7.1. FDA Inspections

7.2. Batch Records

7.3. Annual Product Review

7.4.

7.5.

7.6.

Opinion

8. Declaration

Approach

- Add Requirements
- Redundancy
- Batch Records
  - Provide a stand-alone document that …
  - Reviewed
  - Explain issues
-

APPENDIX A THE QUALIFICATIONS

APPENDIX X REFERENCES CITED

APPENDIX X EVALUATION OF FDA ADVERSE FINDINGS (X – THROUGH Y DATE)

SPYGLASS GROUP CONCLUSION

- cGMP Systems – The FDA identified every significant cGMP System Category in the cGMP regulation as grossly noncompliant
- Systematic Approach - After being notified of serious violations – there was no systematic corrective action
- Management's Lack of Action - Repeated violations indicate that Management either ignored or were ignorant of the legal requirements of the cGMP regulations
- Qualified Quality Management - Not aware of any Quality Professional that would have allowed their organization to repeatedly ignore the FDA's strong messages
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1. FDA 483 – E. Main St. Little Falls – Dated 2/8/06	- Inadequate investigation of complaints – three (3 instances - Inadequate Complaint Procedure -	-	-Control procedures are not established to validate the performance of manufacturing processes – two (2) examples	-	- Adverse drug experience (ADE) information has not been reported to the FDA - Adverse drug experiences not investigated - Adverse drug experience information not reviewed - Some ADEs were not reported to the FDA - Procedures not established for post marketing ADEs
2. FDA 483 – E. Main St. Little Falls – Dated 8/10/2006	QA failed to prevent the release of lots that had significant nonconformances, including: - Incomplete lab data - Batch that failed to meet specification - Batch record deviations - Manufacturing deviations QA filed to detect significant discrepancies in Quality reports and records, five (5) instances include: - Stability testing	-Examples of inadequate equipment preventive maintenance program	-Inadequate validation of the cleaning procedures for manufacturing equipment -Inadequate inprocess testing for four (4) instances -Deviations from production and process control procedures not justified for three (3) instances -Master product and control records are incomplete -Equipment qualification issues -Rejected in-process are not identified and controlled properly	-Seven (7) different product Quality Testing records were incomplete – Examples: -Changes entered into lab notebooks after it was approved -Original out of specification results for three (3) different products were not recorded -Lab computer system was not validated -	

	- Process Validation - Batch record Batch failures not investigated - Stability testing - Lab testing - Active ingredient uniformity of tablets Stability Testing Protocol not followed -		-Inadequate storage practices for chemical raw materials -Chemical raw material handling procedure not followed		
3. Warning Letter – E. Main St. – Little Falls – Dated 8/15/2006	FDA stated that Actavis: -"Several of the observed deficiencies were long-standing, and there is no indication of how or why the lack of compliance was not identified by your firm" -"why it was allowed to continue for such an extended period of item" -"Does your firm have any insight into this situation"? -Prior response to the FDA"does not include details that were discussed during the inspection." -Prior response does not identify the cause of the observed deficiencies with regard to postmarking reporting requirements				
4. Mylan Audit Dated 12/04/06	-Shortage of qualified personnel	-Dated equipment -Warehouse leaking water -Ventilation system smelled of mildew	-	-Quality Control Lab congested	-
5. Revised Warning Letter – E. Main St. Little Falls - Dated 2/1/2007	-Summarized the prior observations and emphasized the seriousness of the noncompliant observations -Actavis Corrective Action and is in disagreement: o FDA stated "In fact, we do not agree with assertions in you August 29 and 30, 2006 letter that certain of the observations listed on the FDA 483 are not accurate" o "..we are concerned about the quality of the of drug products that have been released from your facility under the serious lack of cGMP controls found during the inspection." o "Your response provides no assurance that the records and conditions of manufacture and testing of each such lot of drug products released and marketed by our firm will be evaluated to assure that the released drug products have their appropriate, identity, strength, quality, and purity.				
6. FDA 483 – E. Main St. Little Falls – Dated 9/28/2007	-	-	-Approved production and process procedures not followed	-Stability Testing Protocol not followed	-FDA required – Field Alert Report not submitted on time

7. **FDA 483 – Riverview Drive – Dated 5/20/2008**	-Procedures not followed -Responsibilities not followed -Released products not meeting specifications -Four (4) examples of not investigation products out of specification results -Four (4) examples of inadequate investigation into unexplained discrepancies	-	-	-Eleven (11) instances where products did not meet specifications throughout the products labeled shelf life -Five (5) examples of lab controls do not include scientifically sound test procedures	-
8. **Actavis 5/20/2008 Memo to Senior Management – Summarizing the FDA Inspection**	FDA Inspector stated "One person was signing of in multiple location and the batch (this occurred on the Digoxin double tablet Investigation – The FDA Inspector considered it a very important Observation – additional review of this Investigation may have stopped the release of the batch FDA inspector stated that "from a Quality Systems standpoint, there was a Total Failure". Issues and needs (from FDA inspector): - Do not fix broken systems – get new systems - (Need) Improved	-	FDA inspector stated that: -"premature to be releasing product" -"concerned about product still on the market that was made in Little Falls using similar systems that had failed" -"concern about the 48 products with no impurity profile"	-	-

	infrastructure - Personnel - (Need) Philosophical Change - Investigations on the (past) 483 still not complete - Health hazards on recalls are delinquent - "Get very nervous when you tell us that you are releasing product using current Quality Systems -					
9. Permanent Injunction	-Inspected the firms facilities in Totowa, Little Falls and Taft Rd a total of eight (8) times. The FDA stated: -"drugs are adulterated" -"Interstate commerce drugs that are misbranded" -Introduce or deliver "new drugs that are neither approved" per regulations -"FDA's five inspections of Actavis Totowa's facilities over the last three years have revealed numerous and recurring violations of the current cGMP requirements for drugs"					
Depositions	-	-	-	-	-	
	-	-	-	-	-	
	-	-	-	-	-	
	-	-	-	-	-	